Review

A review of sleep research in patients with spinal cord injury

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Study design: Systematic review.

Objectives: Sleep disturbances are a common complaint among individuals with spinal cord injury (SCI) and were not usually present before the SCI. Their sleep disturbances, including disrupted sleep, spasms, and problems with initiating and sustaining sleep through the night, affect SCI individuals' overall quality of life due to excessive tiredness and low energy levels during the day. Despite the high prevalence of sleep complaints in this population, current knowledge about sleep in the SCI population has not been systematically assessed.

Setting: Capital Region of Denmark.

Methods: We systematically reviewed literature identified from the PubMed and EMBASE databases following PRISMA guidelines.Thirty-seven articles met our inclusion criteria, as only controlled studies were included. This could be a comparison of (1) SCI individuals and able-bodied controls, (2) cervical with thoracolumbar SCI individuals, or (3) cervical, thoracolumbar SCI individuals and able-bodied controls.

Results: Individuals with SCI have a higher prevalence of sleep-disordered breathing and periodic leg movements during sleep (PLMS), lower heart rate, but no nocturnal lowering of blood pressure. 24-hour energy expenditure and sleeping metabolic rate were significantly lower, and bowel movements were altered. Endocrine alterations were found in investigations of melatonin, cortisol and antidiuretic hormone. Questionnaires revealed a high prevalence of subjectively poorer sleep quality in individuals with SCI compared with able-bodied controls.

Conclusions: There are significant differences between groups with SCI and able-bodied controls. SCI objectively and subjectively markedly affects an individual's sleep.

Keywords: Spinal cord injury, Sleep, Sleep apnea, Melatonin, Sleep quality

Introduction

Spinal cord injury (SCI) affects individuals at different spinal cord levels and with varying severity. Depending on lesion location and completeness, affected individuals experience varying degrees of motor, sensory and autonomic impairments and challenges.

In addition to these problems, individuals with SCI often suffer from other complaints, including sleep disturbances. Individuals with SCI may experience disrupted sleep, problems with initiating sleep, waking up during the night, sleep disordered breathing (SDB), nocturnal motor spasms, as well as daytime complaints such as daytime sleepiness and a lack of energy, all of which affect their overall quality of life.[1,2]

In this review, we describe the nature and type of sleep complaints and disorders in SCI populations. We evaluate the magnitude of the problem and identify potential underlying physiological mechanisms.

In recent years, there has been an increasing focus on the effect of sleep disorders on general health, including the population of individuals with SCI. Many studies

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have investigated various aspects of individuals' sleep. One review, by Giannoccaro *et al.*[3] in 2013, assessed sleep disorders in individuals with SCI, but until now, the various parameters regarding sleep disorders and many other physiological changes have not been identified or compared. The present review aims to redress this for the benefit of future researchers within the field, and thereby help individuals with SCI who suffer from sleep problems.

Methods

Search strategy

We conducted a systematic review of the literature following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[4] on June 28th 2016. Updated searches were performed on March 19th 2017, but no additional studies met the inclusion criteria.

Searches were conducted of the PubMed and EMBASE databases with the following inclusive search strategies:

- In PubMed: **((“Spinal Cord Ischemia"[Mesh] OR “Spinal Cord Vascular Diseases”[Mesh] OR “Spinal Cord Neoplasms”[Mesh] OR “Spinal Cord Diseases”[Mesh] OR “Spinal Cord Injuries”[Mesh] OR “Spinal Cord Compression”[Mesh] OR “Central Cord Syndrome”[Mesh] OR “Paraplegia”[Mesh] OR “Paraparesis”[Mesh] OR “Quadriplegia”[Mesh] OR “Brown-Sequard Syndrome”[Mesh] AND “Sleep”[Mesh]**
- In EMBASE: **Spinal Cord Ischemia OR Spinal Cord Vascular Diseases OR Spinal Cord Neoplasms OR Spinal Cord Diseases OR Spinal Cord Injuries OR Spinal Cord Compression OR Central Cord Syndrome OR Paraplegia OR Paraparesis OR Quadriplegia OR Brown-Sequard Syndrome AND Sleep**

No automatic filters were applied to the searches. The search strategy was developed in cooperation with VH, FBS and PJ, and was guided by a medical liaison librarian. Studies were independently analyzed for inclusion by VH and FBS, based on the criteria outlined below.

Inclusion and exclusion criteria

We included studies with all types of SCI, regardless of their etiology and individuals' sex and age, to investigate the relationship between the injury and sleep. Only controlled studies accessible as full articles were included. The control enabled the comparison of two groups: with (1) SCIs (cervical (cSCI) *vs* thoracolumbar SCIs (tSCI)), (2) SCI (cervical (cSCIG) and/or thoracolumbar (tSCIG)) and able-bodied controls, and (3) all three groups (cervical and thoracolumbar SCI and able-bodied controls). Studies that did not yield data for each separate comparable group were excluded. Finally, studies with fewer than three participants in each comparison group, and studies in languages other than Danish, English and French were excluded.

Articles were included after screening the title and, if necessary, the abstract. The remaining results were obtained in full-text format and screened once more against the inclusion criteria by VH and FBS. The reference lists of relevant articles were screened for additional relevant material.

Data extraction

In order to organize the identified articles and collect as much information as possible, we focused on the following characteristics:

(i) Physiological characteristics: e.g. hormone levels, blood pressure (BP), heart rate (HR), oxygenation during sleep, etc.
(ii) Sleep characteristics: sleep stages, sleep quality and other classified sleep variables, e.g. total sleep time (TST), sleep latency (SL), wake after sleep onset (WASO), etc.
(iii) Questionnaire data: subjective sleep quality investigated by questionnaires.

Results

The final searches identified 213 articles in PubMed and 539 articles in EMBASE, from which 18 and 23 articles, respectively, were initially deemed eligible. Additionally, one new article that had not yet been indexed but was found in PubMed, and one article that was not identified in the searches but which still met our inclusion criteria, were included afterwards. Six articles were identified in both databases. Therefore, 37 articles were included (Figure 1 and Table 1).

Various physiological outcomes reported in the studies have been investigated (Table 2). Six studies assessed endocrine levels in relation to sleep, and melatonin was assessed in five of these studies. One also evaluated antidiuretic hormone (ADH) during sleep and various urinary parameters. Ten studies investigated apnea in SCI populations (Appendix 1, supplementary information). Eight studies investigated other respiratory and hemodynamic outcomes in different ways. Finally, one study investigated colonic activity, two studies covered nocturnal penile tumescence, one study addressed actigraphic activity, and one study assessed medical complications.

Various questionnaires were used and were evaluated in different ways (Table 2).

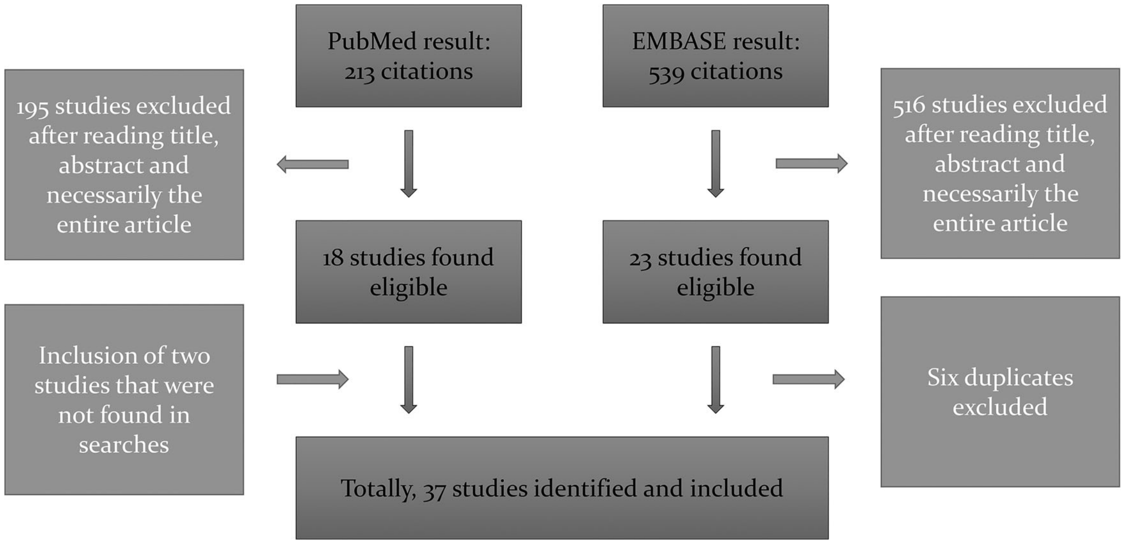

Figure 1 Diagram showing the selection process of included studies.

Characteristics of studies

Physiological studies: study sample sizes varied from 11 to 244 participants. The percentage of males ranged from 51% to 100%; 13 of the 27 studies investigated only male individuals. Five studies included solely individuals with traumatic injuries,[14,16,23,24,26] four studies included traumatic and non-traumatic lesions[18,19,31,38] and the remaining 18 studies did not capture etiological information.

When applicable —in six studies[6,17,20,21,25,27]— a large majority of the participants had complete injuries, either Frankel class A[39] or American Spinal Injury Association Impairment Scale (AIS)[40] grade A. Five studies[9,19,20,22,38] investigated individuals with different grades of impairment. None of the remaining studies provided information about impairment grade; though, in four of these[14,23,29,41] it was interpreted as being either complete or incomplete impairment, or a complete loss of motor and sensory function.

Questionnaire studies: study sample sizes varied from 18 to 822 participants, and all studies but one[37] had a large majority of male participants. The etiology of SCI was primarily traumatic in this subgroup of studies. Most of these study samples included paraplegic and tetraplegic individuals.

Physiological data

Polysomnography assessment of sleep in SCI individuals

The gold standard in assessing sleep is a polysomnography (PSG) study. Ten studies were based on PSG (Appendix 2, supplementary information). Outcomes of the studies included varying hemodynamic outcomes such as heart rate (HR) changes, oxygen saturation (SaO_2) values, the presence of periodic leg movements (PLM) and apnea during sleep.

Periodic leg movements. The two PSG studies investigating PLM during sleep [9,16] found that PLM indexes were higher in SCI individuals than in healthy controls.

Proserpio *et al.*[9] enrolled 15 tetraplegic and 20 paraplegic individuals and found that 28.6% had PLM during sleep (PLMS) in the first year post-injury, and PLM were significantly more frequent in individuals with an incomplete than in those with a complete motor lesion ($P = 0.013$).

Telles *et al.*[16] investigated the prevalence of PLM and Restless Legs Syndrome (RLS). RLS was found in 100% of the SCI group (SCIG) and in 18.3% of the control group (CG). The PLM index was significantly higher in the SCIG than in the CG, and a PLM index >5 was found in 31.3% and 75.0% of CG and SCIG, respectively. They found no significant difference between controls and SCI individuals in the PLM arousal index (i.e. the number of PLM per hour of sleep associated with EEG arousal), or between paraplegics and tetraplegics in this regard. However, there was a tendency for tetraplegic individuals to have more PLM arousals compared with paraplegics and controls.

Oxygenation. Oxygenation was investigated in three PSG studies.[9,12,28] Cahan *et al.*[28] evaluated the oxygenation level during sleep in 16 tetraplegic individuals and 12 healthy controls . The tetraplegics were divided into two subgroups; 10 with values within the normative range established by the healthy group, and six with

Table 1 Articles selected for review, grouped as physiological or questionnaire studies, with the methods used. Articles containing physiological data and patient-reported data are presented in both categories with the respective methods listed.

Physiological studies

First author and year of publication	*Number of participants*	*Methods*
Wijesuriya *et al.*[5]	Eight cSCI individuals and six able-bodied controls	Choanal pressure recordings to assess awake nasal resistance Anterior rhinomanometry
Fatima *et al.*[6]	22 cSCI individuals and 22 able-bodied controls	Serum cortisol and melatonin sampling
Tobaldini *et al.*[7]	12 cSCI individuals, 17 tSCI individual and eight able-bodied controls	PSG, i.e. *EEG; ECG; Chin EMG;* Nasal airflow measurement
Kostovski *et al.*[8]	Six cSCI individuals and six able-bodied controls	Measurements of plasma melatonin and several hemostasis markers
Proserpio *et al.*[9]	15 tetraplegic and 20 paraplegic individuals	Clinical assessment PSG Arterial blood gas analysis
Iversen *et al.*[10]	Six tetraplegic individuals and six able-bodied controls	Assessment of melatonin and thrombin using Calibrated Automated thrombogram
Bascom *et al.*[11]	Ten tetraplegic individuals, eight paraplegic individuals and 17 able-bodied controls	PSG
Sankari *et al.*[12]	Eight cSCI individuals, eight tSCI individuals and 16 able-bodied controls	Hypocapnic apneic threshold and CO2 reserve assessed using NIV PSG
Sankari *et al.*[13]	Eight cSCI individuals, eight tSCI individuals and eight able-bodied controls	PSG
Verheggen *et al.*[14]	Six cSCI individuals, nine tSCI individuals and ten able-bodied controls	Salivary melatonin sampling
Le Guen *et al.*[15]	25 tetraplegic individuals and 219 able-bodied controls	Diagnostic and CPAP titration polysomnograms
Telles *et al.*[16]	Eight SCI individuals and 16 able-bodied controls	PSG
Thijssen *et al.*[17]	Eight tetraplegic individuals, seven paraplegic individuals and eight able-bodied controls	Measurements of intestinal core temperature (telemetric) and physical activity
Ancha *et al.*[18]	Eight SCI individuals and six able-bodied controls	Colonic manometric studies
Spivak *et al.*[19]	21 tetraplegic individuals and 20 able-bodied controls	Actigraphy
Scheer *et al.*[20]	Three cSCI individuals, two tSCI individuals and ten able-bodied controls	Melatonin sampling Scoring of respiratory events PSG
Suh *et al.*[21]	Nine cSCI individuals and nine tSCI individuals	RigiScan (two consecutive nights)
Burns *et al.*[22]	12 tetraplegic individuals and eight paraplegic individuals	ESS; Physiological parameters
Casiglia *et al.*[23]	11 SCI individuals and 11 able-bodied controls	BP, HR and leg flow measurement
Demirel *et al.*[24]	Ten tetraplegic individuals, ten paraplegic individuals and ten able-bodied controls	Cardiac parameters
Kilinç *et al.*[25]	Eight tetraplegic individuals, eight paraplegic individuals and eight able-bodied controls	Urinary parameters
Bunten *et al.*[26]	Six tetraplegic individuals, seven paraplegic individuals and thirteen able-bodied controls	HR variability
Monroe *et al.*[27]	One tetraplegic individual, nine paraplegic individuals and 59 able-bodied controls	24-hour respiratory chamber metabolic measures
Cahan *et al.*[28]	16 tetraplegic individuals and 12 able-bodied controls	24-hour pulse oximetry recording
Lamid S.[29]	12 tetraplegic individuals and 12 paraplegic individuals	American Medical System (AMS) Nocturnal Penile Tumescence Monitor (NPTM)
Braun *et al.*[30]	Seven cSCI individuals and four tSCI individuals	Respiratory evaluations
Shimizu *et al.*[31]	Three controls, 11 individuals with supraspinal lesions and 11 individuals with spinal lesions	Investigation of H reflex during sleep

Continued

Table 1 Continued.

Physiological studies

Questionnaire studies		
Article	*Number of participants*	*Methods*
Spong *et al.* [32]	163 tetraplegic individuals	Demographic questions; Karolinska Sleepiness Scale (KSS); Basic Nordic Sleepiness Questionnaire; Functional Outcomes of Sleep Questionnaire (FOSQ); Multivariate Apnoea Prediction Index and Assessment of Quality of Life (AQoL) Questionnaire
January *et al.* [33]	1oo tetraplegic individuals and 77 paraplegic individuals	PSQI; 12-item Short-Form Health Survey (Version 2); Beck Anxiety Inventory and Individual Health Questionnaire; Satisfaction With Life Scale
Sankari *et al.* [12]	Eight cSCI individuals, eight tSCI individuals and 16 able-bodied controls	ESS
Verheggen *et al.* [14]	Six cSCI individuals, nine tSCI individuals and ten able-bodied controls	PSQI; ESS
LaVela *et al.* [34]	822	Cross-sectional survey
Saurat *et al.* [35]	15 tSCI individuals and 15 able-bodied controls	Dream assessment: interviews with psychologist, dream content analyses and cognitive, psychological and sleep tests (PSQI)
Telles *et al.* [16]	Eight SCI individuals and 16 able-bodied controls	ESS; IRLS Scale Rating Scale
Spivak *et al.* [19]	21 tetraplegic individuals and 20 able-bodied controls	Mini Sleep Questionnaire
Norrbrink Budh *et al.* [36]	95 tetraplegic individuals and 97 paraplegic individuals	BNSQ
Dannels *et al.* [37]	230	Questionnaire on perimenopause-related symptoms
Suh *et al.* [21]	Nine cSCI individuals and nine tSCI individuals	International Index of Erectile Function Questionnaire
Burns *et al.* [38]	282 tetraplegic individuals and 302 paraplegic individuals	Medical reports to assess: *Sleep apnea diagnosis; Demographic information; Neurological characteristics; Treatments*
Biering-Sørensen *et al.* (1)	192 cSCI individuals, 216 tSCI individuals and 339 able-bodied controls	BNSQ
Burns *et al.* [22]	12 tetraplegic individuals and eight paraplegic individuals	ESS
Hyyppä *et al.* [2]	80 paraplegic individuals compared with several groups featuring other chronic diseases	Questionnaire on sleep habits; Beck Depression Inventory

SCI, spinal cord injury; cSCI, cervical spinal cord injury; tSCI, thoracic spinal cord injury; BP, blood pressure; ECG, electrocardiography; EEG, electroencephalography; EMG, electromyography; ESS, Epworth Sleepiness Scale; HR, heart rate; IRLS, International Restless Legs Syndrome Scale; PSG, polysomnography; PSQI, Pittsburgh Sleep Questionnaire Index; NIV, noninvasive ventilation; BNSQ, Basic Nordic Sleep Questionnaire.

oxygen saturation (SaO_2) profiles below this normative range. The six tetraplegic individuals spent 70% of the recorded time with an SaO_2 lower than the normal range ($P < 0.05$). Five of the six hypoxic tetraplegics had a medical history of snoring and increased daytime sleepiness compared with six of the 10 normoxic tetraplegics.

Sankari *et al.*[12] found no significant difference in wake SaO_2 between their eight tetraplegic individuals (95.9 ± 1.3) and their group of eight paraplegic individuals (96.6 ± 1.0). No value was reported for the CG.

Proserpio *et al.*[9] found significantly higher oxygen desaturation indexes when comparing cSCI individuals (16.0 events/hour) with controls (2.4 events/hour).

Apnea. Ten studies investigated sleep apnea (Appendix 1, supplementary information). All but one[28] of the eight PSG[5,9,11–13,15,20,28] studies investigating apneic events found significant differences when comparing SCI individuals with healthy controls. Two studies assessing sleep apnea using methods other than PSG found a high prevalence of apnea in SCI individuals with high motor levels.[22,38] Some of the more specific results are described below.

Sankari *et al.*[13] investigated whether SCI levels affect upper airway collapsibility and neuromuscular compensatory responses to obstruction, since sleep-disordered breathing (SDB) is more prevalent in individuals with SCI than in the general population. The ventilation, timing, upper airway resistance and pharyngeal collapsibility were determined during non-rapid eye movement (NREM) sleep. The researchers found that cSCI individuals had lower median ventilation and required the same holding pressure values to eliminate flow limitation in comparison with tSCI and control individuals. Furthermore, the critical closing pressure of the upper

Table 2 Physiological studies not validated by PSG and questionnaire studies. Individual characteristics, main outcomes and results are shown.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Endocrinology					
Scheer *et al.*[20]	15 (87)	N/A	Three C4-7, one T4, one T5 (Complete (Frankel class A))	- Melatonin rhythm - Cortisol/TSH rhythm - AHI	- Absent melatonin rhythms in tetraplegics - Conserved melatonin rhythm in paraplegics - TST and SE significantly lower in tetraplegics - REM sleep latency significantly prolonged in tetraplegics - No significant differences in sleep onset latency or proportions of different sleep stages between groups - No SCI individuals had PLMS - One SCI individual in each group had mild sleep apnea
Kostovski *et al.*[8]	12 (100)	N/A	C5-8 (N/A)	- Double-blind, randomized, placebo-controlled crossover study of melatonin - Assessment of hemostatic factors (factor VIIa, free TFPI antigen, VWF and D-dimer)	- Melatonin supplementation can nearly restore 24-h profile in stable tetraplegic individuals - Placebo cannot restore normal 24-h profile of melatonin - The tetraplegic groups (melatonin and placebo group) showed similar 24-h patterns of F_{1+2} and D-dimer, but F_{1+2} was significantly increased compared with CG levels - D-dimer similar across the three groups - No significant differences in FVIIa among groups - Decreased VWF in CG during night compared with SCIG - No significant changes in free TFPI antigen among groups

Continued

Table 2 Continued.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Fatima *et al.*[6]	44 (100)	N/A	Cervical (Complete (Frankel class A))	- Serum melatonin and cortisol levels	- No significant difference in melatonin levels during afternoon and evening - Significantly higher melatonin levels in SCIG during morning hours - Significantly lower melatonin levels in SCIG during night hours - A significant difference between CG and SCIG in circadian melatonin rhythm - No significant difference in cortisol levels during morning and afternoon - Significantly higher cortisol levels in SCIG during evening and night - A significant difference between CG and SCIG in circadian cortisol rhythm
Verheggen *et al.*[14]	25 (100)	Traumatic	Nine thoracic and six cervical (Motor and sensory complete)	- Salivary melatonin levels	- No change in melatonin level in cSCIG - cSCIG did not reach DLMO threshold - tSCIG and CG with comparable increases in melatonin levels - tSCIG and CG with comparable DLMO
Kilinç *et al.*[25]	24 (71)	N/A	Eight at T6 and above (group I) Eight below T6 (group II) (16 AIS A)	- ADH - Urinary parameters	- No significant differences between day and night urine output rates in groups I and II - Significantly lower urine output in CG during night - No significant differences in ADH levels from day to night in group I and II - Significant increase in ADH during night in CG - No significant changes in urine osmolality from day to night in group I and II - Significantly higher urine osmolality in CG during night

Continued

Table 2 Continued.

Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Non-PSG physiological results					
Iversen *et al.*[10]	12 (100)	N/A	C5-8 (Complete)	- Randomized placebo-controlled crossover study with melatonin supplementation while investigating the endogenous thrombin potential (ETP)	- A significant lack of a diurnal pattern of indices of thrombin generation - Supplementation of melatonin tended to decrease ETP normalized values (P = 0.073) in tetraplegic men compared with those given placebo - Normalized values for ETP were similar (P > 0.05) in able-bodied and tetraplegic males receiving melatonin - Compared with tetraplegic males receiving placebo, able-bodied men had lower normalized ETP values (P = 0.019)
Respiratory and hemodynamic values					
Thijssen *et al.*[17]	23 (100)	N/A	Eight cervical, seven thoracic (15 AIS A)	- Core body temperature assessment - HR - Sleep reports	- CG demonstrated typical circadian variation in Tcore - In SCIGs, circadian Tcore variation depended on lesion level - A significant impact of time-of-day for Tcore reactivity was found - In tetraplegics, the relation of Tcore to physical activity changed markedly 4–10 hours after sleep, consistent with early afternoon increase in Tcore in tetraplegics, despite little change in physical activity
Le Guen *et al.*[15]	244 (74)	N/A	25 cervical (N/A)	- Comparison of AHI, effective CPAP levels, age and BMI among acute tetraplegic group, chronic tetraplegic group and able-bodied CG	- Lower BMI in acute SCIG than CG, but not lower than in chronic SCIG - No significant BMI difference between chronic SCIG and CG - CG required higher CPAP levels to abolish OSA than did acute and chronic SCIG - No significant difference in CPAP levels between acute and chronic SCIG - In CG: a linear correlation between increasing AHI and BMI as well as the CPAP level required to treat OSA - In SCIGs, no significant correlation between AHI and BMI or AHI and CPAP levels was found

Continued

Table 2 Continued.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Sankari *et al.*[12]	32 (56)	N/A	Eight cervical, eight thoracic (N/A)	- Tidal volume - End-tidal CO_2 and O_2 - Supraglottic pressure	- No significant difference among the three groups (CSCI, TSCI, CG) in the hypocapnic chemoreflex sensitivity - A narrower CO_2 reserve in CSI than in the two other groups - No difference in end-tidal CO_2 between groups
Casiglia *et al.*[23]	22 (73)	Traumatic	Five at C7 and above Six at T2 and below (N/A, but all SCI individuals had complete loss of sensory and motor functions in the legs)	- BP - HR - Leg hemodynamics - Forearm hemodynamics	- No nocturnal BP decrease in SCIG, whereas CG showed a significant nocturnal BP fall (24%, P = 0.001) - SCIG had lower 24-h HR values than CG - A significant circadian rhythm of leg resistance in CG with lower values during sleep (P = 0.001) - No day/night difference in SCIG in leg flow and resistance - Forearm flow showed same trend in CG as in tSCIG. In cSCIG, no trend of forearm flow was detectable
Bunten *et al.*[26]	26 (100)	Traumatic	Six cervical and seven thoracic/lumbar (N/A)	- Three types of HRV analysis: 1) Time domain analysis 2) Amplitude spectral analysis 3) Power spectral analysis	1) No significant differences between groups in time domain analysis 2) Significant differences found between groups over 24 hours and during sleep (P = 0.03 and P = 0.04, respectively, and no significant difference between paraplegic and tetraplegic means) in mean values of LF amplitude 3) Overall, the same results were obtained when performing the power spectral analysis

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Table 2 Continued.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Monroe *et al.*[27]	69 (100)	N/A	C6-L3: nine paraplegics and one tetraplegic individual (Complete (Frankel class A))	Respiratory chamber metabolic values: - 24-h EE - Spontaneous physical activity - RMR - SMR - DXA scan for all in SCIG and for 33 in CG	- 24-h EE, spontaneous physical activity ($P < 0.01$), RMR ($P < 0.01$), TEF and SMR ($P < 0.05$) significantly lower in SCIG than in CG
Demirel *et al.*[24]	30 (53)	Traumatic	Ten cervical, eight thoracic, two lumbar (Ten AIS A, nine AIS B and one AIS C)	- Evaluation of autonomic nerve system function with HRV on a minimum of 18 hours of ECG recording including the whole night	- No difference between groups (CG, paraplegics and tetraplegics) for the frequency of ventricular or supraventricular ectopics, minimal and mean HR and the longest RR interval - Maximum HR was lower in the cSCIG than in CG - HR wake-sleep changes preserved in all groups - When examining by completeness in the cSCIG, in incomplete cases HF and TP showed the physiological sleep-wake cycle, and circadian HR changes were also preserved - In complete tetraplegia, the rhythm of circadian HR changes was blunted, but was not statistically significant ($P = 0.08$)
Burns *et al.*[22]	20 (100)	Two non-traumatic, 18 traumatic	12 cervical, eight thoracic/lumbar (Eight tetraplegics with AIS A or B, four tetraplegics with AIS C or D, six paraplegics with AIS A or B, and two paraplegics with C or D)	- Overnight cardiopulmonary study to investigate sleep apnea syndrome	- Sleep apnea diagnosed in 58% of tetraplegics, but only in 12.5% of paraplegics ($P = 0.07$) - Sleep apnea diagnosed in 21% with motor-complete injuries and in 83% with motor-incomplete injuries ($P = 0.018$) - No difference in mean oxygen saturation while awake between individuals with and without apnea

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Table 2 Continued.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Other					
Ancha *et al.*[18]	14 (100)	Six traumatic, one cervical stenosis and one transverse myelitis	Three tetraplegics and five paraplegics (N/A)	- Colonic ambulatory manometric studies	- HAPC absent in the SCIG during pre-sleep, sleep and post-sleep - In the CG, the numbers of HAPC/h were as follows: pre-sleep phase, 2.0 ± 0.4; sleep phase, 0.8 ± 0.2; and post-sleep phase, 10.5 ± 2.0 - A significant increase in the number of HAPC from sleep to post-sleep phases was noted (0.8 ± 0.2 *vs.* 10.5 ± 2.0, $P < 0.005$)
Suh *et al.*[21]	18 (100)	N/A	Nine paraplegics and nine tetraplegics (18 AIS A)	- International Index of Erectile Function Questionnaire - RigiScan (2 nights)	- 8/9 and 3/9 with cervical and thoracic injury, respectively, had nocturnal penile tumescense (NPT)
Lamid *et al.*[29]	24 (100)	N/A	12 paraplegics and 12 tetraplegics (N/A, but 16 complete lesions and eight incomplete lesions)	- Nocturnal Penile Tumescence Monitor (NPTM) overnight	- A significant ($P < 0.01$) difference in mean duration between paraplegics and tetraplegics: 4.75 and 14.9 minutes, respectively, - A significant ($P < 0.01$) difference in mean increase of penile circumference, which was greater in tetraplegics - No difference in NPT between complete and incomplete lesions
Spivak *et al.*[19]	41 (66)	16 traumatic, five non-traumatic	21 tetraplegics: nine C4, ten C5, one below C6, one below C7 (Eight AIS A, eight AIS B, five AIS C)	- Actigraphic movement index (MI), total sleep time (TST), sleep efficiency (SE), wake after sleep onset (WASO), sleep latency (SL), and NOA	- A significant high correlation between head-mounted and wrist actigraph measurements, including those of TST, SL, MI, WASO, and SE in their CG - In the SCIG: different findings for individuals with injury below the C5–C7 level and those with injury below the C4 level. With injury below the C4 level, the head moved more than the hand during sleep, as opposed to both CG and SCI at level C5-C7, where the hand moved more than the head during sleep. - Significant differences found in the group with SCI below C4 between head and wrist actigraphic findings in all the sleep measures except SL and NOA

Continued

Table 2 Continued.

Non-PSG physiological results **Study**	**Number of participants (% male)**	**Types of lesion**	**Level and severity of lesion**	**Main outcomes**	**Results**
Shimizu *et al.*[31]	25 (80)	Varying diseases and trauma	N/A (11 individuals with different spinal lesions)	- All night recordings of EEG, horizontal eye movements, EMG of the mental muscle and H reflex of the calf muscle	- In normal subjects, the H reflex is depressed during REM sleep. - In individuals with almost complete transverse spinal lesions, the H reflex persisted during REM sleep. - Results from the group with partial spinal lesions suggest that the descending pathways responsible for the depression of H reflex during REM sleep run mainly along the anterior funiculi and the anterior halves of the lateral funiculi.
Questionnaire results					
Study	*Number. of participants (% male)*	*Types of lesion*	*Sites of lesions*	*Scale/questionnaire and main outcomes*	*Results*
January *et al.*[33]	177 SCI individuals and 52 controls (62 in the SCIG, N/A for CG)	Primarily traumatic, 11.3% medical/surgical, 1.1% other	100 cervical, 77 presumably thoracic	- PSQI - 12-item Short-Form Health Survey (Version 2) - Beck Anxiety Inventory and Individual Health Questionnaire - Satisfaction With Life Scale - Assessment of participants' sleep, mental and physical health, and psychosocial well-being	- On the PSQI, the mean score in the SCIG was 6.31 compared with 2.67 in the CG ($P < 0.001$) - Sleep difficulties were common: 51.4% of participants reported sleep problems during the previous month - Age and tetraplegia were significantly associated with poor sleep - Sleep quality could explain a small but significant proportion of the variance in depression, anxiety, but not in that of life satisfaction

Continued

Table 2 Continued.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Saurat *et al.*[35]	30 (86.7)	Five with congenital paraplegia, ten tSCI individuals	N/A	- PSQI - Free and Cued Selective Reminding Test - Symptom Check List-90-R - Dream collection over six weeks - Dream Content Analysis - Comparison of dreams containing various motor skills in congenital paraplegia, acquired paraplegia and able-bodied controls	- PSQI-scores not reported - Almost all paraplegic individuals walk in their dreams, just as much as do able-bodied individuals - Their results reinforce the concept that the human brain has an inner walking program, which is either genetic or developed through mirror neurons
Verheggen *et al.*[14]	25 (100)	Traumatic	Six cervical, nine thoracic	- PSQI - ESS - Assessment of salivary melatonin while investigating individual sleep quality	- Tetraplegics and paraplegics tended to report poorer sleep quality than did CG (P = 0.06) - The prevalence of poor sleep was significantly higher in the SCIG than in the CG (P = 0.02) - Though not statistically significant, the tetraplegics reported the highest mean scores and prevalence of excessive sleepiness on the ESS
Sankari *et al.*[12]	32 (56)	N/A	Eight cervical, eight thoracic	- ESS - Investigations of SDB	- Mean ESS scores of 11.0 (±4.4), 10.3 (±4.0) and 4.7 (±2.7) were obtained for cSCI, tSCI and CG, respectively
Telles *et al.*[16]	24 (100% male in SCIG, 50% in CG)	Traumatic	Three cervical, five thoracic	- ESS - IRLS Scale Rating Scale - Investigations of PLMS and RLS in ASIA A SCI individuals	- No difference of diurnal somnolence between groups according to the ESS
Burns *et al.*[22]	20 (100)	18 traumatic, two non-traumatic	12 cervical, eight thoracic	- ESS - Investigations of sleep apnea	- The mean ESS score was 10.1 (± 7.1) for the group with sleep apnea and 7.3 (± 4.9) for the group without sleep apnea (P = 0.32) - In the entire sample of individuals, ESS scores were not significantly correlated with the apnea index (r = 0.182; P = 0.456) or RDI (r = 0.133; P = 0.586)

Continued

Table 2 Continued.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Spong *et al.*[32]	163 (77)	N/A	Cervical	- Demographic questions - Karolinska Sleepiness Scale (KSS) - Basic Nordic Sleepiness Questionnaire - Functional Outcomes of Sleep Questionnaire (FOSQ) - Multivariate Apnoea Prediction Index (MAPI) - Assessment of Quality of Life (AQoL)	- BNSQ: On 11 of the 14 questions, the current sample was significantly ($P < 0.05$) worse than normal population values. The current sample was better than normal values in BNSQ question 1 (falling asleep; $P < 0.001$), and there was no difference between the samples in BNSQ questions 8 and 10 (excessive sleepiness in the morning and tendency to fall asleep at work). Similarly, the current sample scored significantly worse ($P < 0.05$) than the normal values in five of the seven quantitative questions in the BNSQ* - Multivariate analysis revealed that reduced quality of life was associated with more severe injury, increasing age and worse sleep symptoms on the BNSQ
LaVela *et al.*[34]	822 (94.2% in dysfunctional sleeper group, 96.7% in non-dysfunctional sleeper group)	Veterans	62.2% cervical in dysfunctional sleeper group, 66.1% in non-dysfunctional sleeper group	- Cross-sectional survey. Variables were self-reported and included: veteran demographic and injury characteristics (sex, race, education, age, living arrangement (alone *vs* cohabiting), marital status, injury level (paraplegia *vs* tetraplegia) and duration of injury; behaviors (drinking and smoking status); health-care conditions/complications during the previous year (hypertension, high cholesterol, diabetes, asthma, chronic obstructive pulmonary disease (COPD), pressure ulcers and weight gain)	- Significant associations of sleep dysfunction with weight gain, smoking, alcohol misuse and chronic conditions (COPD, asthma)

Continued

Table 2 Continued.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Spivak *et al.*[19]	41 (66)	16 traumatic, five nontraumatic	Cervical	- Mini Sleep Questionnaire - Assessment of subjective sleep quality while investigating actigraphic sleep variables	- Assessment by MSQ did not show a significant difference in subjective sleep quality between healthy individuals and the SCIG. The average MSQ score was 22.9 (SD = 8.0) in individuals with tetraplegia and 22.1 (SD = 8.4) in healthy individuals. Nevertheless, all the individuals claimed worsening of sleep quality after the spinal cord injury and recalled better sleep quality before the injury: average retrospectively estimated MSQ score of all individuals was 14.25 (SD= 5.4).
Norrbrink Budh *et al.*[36]	191 (54)	N/A	94 cervical, 97 thoracic	- Pain questionnaire - Pain scoring using VAS - Hospital Anxiety and Depression (HAD) Scale - BNSQ - Assessment of sleep quality in SCI individuals with and without pain	- Regarding the reported quality of sleep, tetraplegics rated general sleep quality (Q6) to be poorer than paraplegics (P = 0.051). Individuals with tetraplegia and those with paraplegia had a median value of 2, but the IQRs were wider among tetraplegics [2;3] than paraplegics [1;3]. - No other differences were found in other questionnaire variables between tetraplegic and paraplegic individuals. - Individuals with incomplete injuries reported poorer quality sleep than did individuals with complete injuries: difficulties in falling asleep (Q1) (P = 0.044), awakening during the night (Q3) (P = 0.005), awakening too early in the morning (Q5) (P = 0.020), overall sleep quality (Q6) (P = 0.045), use of sleeping pills (Q7) (P = 0.024), and sleepiness during leisure time (Q11) (P = 0.012).

Continued

Table 2 Continued.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Dannels *et al.*[37]	230 (0)	N/A	44 complete tetraplegics, 71 incomplete tetraplegics, 67 complete paraplegics and 48 incomplete paraplegics	- Questionnaire on perimenopause-related symptoms - Evaluation using a questionnaire regarding symptoms associated with perimenopause, self-rated severity scores of various symptoms, and different options for treatment of the symptoms related to perimenopause	- 43% reported sleep disturbance, 40% reported night sweats - Subjective severity of these symptoms varied, but no significant differences were noted between women with tetraplegia and paraplegia, whether neurologically complete or incomplete - Among the explored symptoms, sleep disturbances had the highest mean severity score (5.36) and night sweats had a relatively high score (4.38)
Suh *et al.*[21]	18 (100)	N/A	Nine cervical, nine thoracic	- International Index of Erectile Function (IIEF) questionnaire - Assessment of the effects of complete SCI on nocturnal penile tumescence	- Of the nine men with cervical injuries, three had one or more “good” nocturnal erections, and one of nine men with thoracic injuries had one or more “good” nocturnal erections
Hyyppä *et al.*[2]	80 (85)	Primarily traumatic	Thoracic	- Questionnaire on sleep - Large investigation of sleep quality in various chronic illnesses, including paraplegia	- Individuals with paraplegia had a later mean awakening time on working days than did their control individuals (07:08 *vs* 06:52; $P < 0.001$; t-test). They slept more per 24-h period than did controls (08:11 *vs* 07:40; $P < 0.001$; t-test). - The other sleep characteristics of the paraplegic individuals differed from those of the control individuals: they suffered from insomnia, long SL, DMS, morning irritability and unwillingness to go to sleep - The biorhythm of paraplegic individuals differed from that of controls: 20% of the individuals described themselves as “early birds” in contrast to 37.5% of the individuals in their CG ($P < 0.001$; Fisher’s exact test).

Continued

Table 2 Continued.

Non-PSG physiological results Study	Number of participants (% male)	Types of lesion	Level and severity of lesion	Main outcomes	Results
Biering-Sørensen *et al.*[1]	747 (74)	Primarily traumatic	193 cervical, 137 thoracic, 78 lumbar	- Nordic Sleep Questionnaire - Evaluation of sleep problems in SCI population and comparisons with large normal population	- Highly significant differences between SCIG and CG (worse in SCIG) in regard to falling asleep, waking more frequently, greater consumption of sleep medication, sleeping more hours, snoring more, taking more and longer naps, and subjectively sleeping worse.

*Compared with Danish SCI and normal population responses.
cSCIG, cervical spinal cord injury group; DLMO, dim light melatonin onset; tSCIG, thoracic spinal cord injury group; CG, control group; N/A, not applicable; HRV, heart rate variability; RMR, resting metabolic rate; SMR, sleeping metabolic rate; TEF, thermic effect of food; HAPC, high-amplitude propagating contractions; NPT, nocturnal penile tumescence.

airways was higher in SCI participants than in the normal population. There was no significant difference in cSCI and tSCI individuals' median resistance of the upper airways compared with the controls. Finally, the authors investigated the inspiratory duty cycle in the three groups. They found a lower median cycle during non-flow-limited breathing in the cSCIG compared with other participants.

Somewhat similar investigations were performed by Bascom *et al.*,[11] who also investigated ventilation, timing and upper airway resistance. They found that SCI individuals experience hypoventilation at sleep onset, and concluded that the hypoventilation could not be explained by upper airway mechanics, but that it might contribute to the development of SDB in these individuals.

Burns *et al.* also investigated sleep apnea in two non-PSG studies. In the first study,[38] they found 42 tetraplegic and 11 paraplegic individuals diagnosed with sleep apnea, representing 14.9% of all tetraplegic and 3.7% of all paraplegic patients, respectively. The apneic tetraplegics had an overall higher motor level ($P < 0.001$), the majority having a level of C4 or C5. Age, years injured, etiology of injury, and spine surgery history did not differ between tetraplegic individuals with and without apnea.

In the second study, Burns *et al.*[22] investigated sleep apnea in chronic SCI individuals. Eight of the 20 individuals were diagnosed with sleep apnea syndrome. Individuals with sleep apnea had a mean apnea index of 17.1 ± 6.9, a mean respiratory distress index of 51.8 ± 16.1, and a mean nadir SaO_2 of 68.6% (range, 61% – 85%). Apneic episodes were predominantly obstructive; however, two individuals demonstrated central apneas with an apnea index of 23.1 and 17.7, respectively, and two individuals had a mixed apnea type with apnea indexes of 19.6 and 21.0. This study compared data based on the presence of apnea, but did not compare paraplegic and tetraplegic individuals. Nevertheless, they reported that sleep apnea was diagnosed in 7 of 12 (58%) individuals with tetraplegia, but only in 1 of 8 (12.5%) individuals with paraplegia ($P = 0.07$).

Non-polysomnographic assessment of physiology in relation to sleep in SCI individuals

Neuroendocrinology

Melatonin and cortisol in SCI individuals. Five studies[6,8,14,20,41] evaluated melatonin in SCI individuals. Other hormone levels were also assessed in four of these studies; one investigated melatonin and cortisol,[6] another investigated melatonin, cortisol and TSH,[20] a third covered melatonin and numerous hemostatic factors,[8] and the fourth study addressed melatonin and the endogenous thrombin potential.[41] Their findings are summarized in Table 2.

Fatima *et al.*[6] investigated cortisol and melatonin in a cSCIG and a CG (Table 2). Overall, there was a significant difference in the circadian rhythm of both melatonin and cortisol between the CG and the cSCIG. The authors found significantly higher melatonin levels in the cSCIG during morning hours but significantly lower equivalent levels during night hours.

Verheggen *et al.*[24] found that melatonin levels in controls and paraplegics were significantly higher than in tetraplegic individuals at the 22:30 and 23:00 time points. The CG and the tSCIG had a comparable increase in melatonin levels, while the cSCIG exhibited no change in melatonin over that period. They also found no significant differences between dim-light melatonin onset in the CG and paraplegic individuals. It was not possible to calculate the dim-light melatonin onset in the tetraplegics because they did not reach the study's dim-light melatonin onset threshold of 4 pg/mL.

Antidiuretic hormone in SCI individuals. Kilinç *et al.*[25] investigated ADH and urinary output in SCI individuals and found significant differences between the two groups of SCI individuals with their CG (Table 2). The CG showed significant increases in ADH during the night, resulting in lower urine output during the night, whereas there were no significant changes in ADH from day to night in the two SCIGs.

Physiological alterations following an SCI. Table 2 illustrates the studies and their physiological changes due to SCIs. The primary findings are briefly summarized below.

Hemodynamics. Casiglia *et al.*[23] investigated 24-hour hemodynamics and found no significant difference between the sleeping period of their CG and SCIG. There was no nocturnal decrease in BP in the SCI individuals, whereas the controls exhibited a significant nocturnal fall in BP. There was no significant variability in BP over 24 hours in the SCI individuals. The SCIG group also had lower 24-hour HR values than able-bodied individuals, although the circadian HR profile was the same in the two groups.

There was a significant circadian rhythm of leg resistance and flow in able-bodied individuals with lower resistance and higher flow values during sleep; conversely, no day/night difference was evident in the SCIG. Regarding forearm hemodynamics, the flow showed the same trend in controls as in the six paraplegic individuals transected below T2. There was a detectable trend in forearm flow in the five tetraplegics injured at C7 or above.

Demirel *et al.*[24] investigated HR variability (HRV) and conducted 24-hour Holter monitoring. They found no differences between the groups in the frequency of ventricular or supraventricular ectopics, minimal and mean HR and the longest RR interval. Maximum HR was lower in the tetraplegics than in the controls (124.1 ± 11.2 *vs.* 139.4 ± 10.9, $P < 0.05$), but HR wake-sleep changes were maintained in all three groups (CG, tSCIG and cSCIG).

Bunten *et al.*[26] also investigated HRV in paraplegic and tetraplegic individuals and controls. Mean values for low-frequency power spectral analysis demonstrated overall significant differences between groups over 24 hours and during sleep. *Post hoc* comparisons revealed significant differences in the means between controls and tetraplegics and between controls and paraplegic individuals. However, no significant differences between paraplegics and tetraplegics were observed, and this finding persisted irrespective of the influence of physical activity.

Energy expenditure. Monroe *et al.*[27] found that 24-hour energy expenditure and sleeping metabolic rate were significantly lower in SCI individuals than in control individuals. However, the CG had significantly more fat-free mass than the SCIG.*Colonic activity*

Ancha *et al.*[18] conducted prolonged colonic ambulatory manometric studies (>24 hours). Their main finding was that high amplitude propagating contractions were absent in the SCIG, but present in the non-SCIG during pre-sleep, sleep and post-sleep.

Nocturnal erectile activity. Suh *et al.*[21] found that nocturnal penile tumescence was more common in individuals with cervical injury (8/9) than in individuals with thoracic injury (3/9).

Lamid *et al.*[29] found a significant difference in mean duration between paraplegics (4.75 minutes) and tetraplegics, (14.9 minutes), as well as a significant difference in the mean increase in penile circumference, the value being greater in tetraplegics. There was no difference in nocturnal penile tumescence between complete and incomplete SCI lesions.

Actigraphic measures. Spivak *et al.*[19] assessed sleep by actigraphy in tetraplegic individuals. They found a significantly high correlation between head-mounted and wrist actigraph measurements, including those of actigraphic movement index, total sleep time, sleep efficiency, wake after sleep onset, and sleep latency in their CG. However, no correlation was observed between head-mounted and wrist actigraph measurements for the number of awakenings.

With injuries below the C4 level, the head moved more than the hand during sleep, as opposed to both CG and SCI below level C5-C7, where the hand moved more than the head during sleep. Significant differences were found in the group with SCI below level C4 between head and wrist actigraphic findings in all sleep measures except sleep latency and number of awakenings.

Questionnaire data

In general, the studies investigating sleep quality in SCI populations tended to report poor sleep quality. Unfortunately, there is no agreement about the best method of assessing general sleep quality, so we report the results obtained from a variety of questionnaires and scales (Tables 1 and 2).

Sleep questionnaires and scales

One of the few questionnaires that has been used more than once is the Pittsburgh Sleep Questionnaire Index (PSQI).[14,33,35] It is a self-rated questionnaire about sleep quality and disturbances over a one-month period that yields seven component scores, based on the scoring of 19 items: subjective sleep quality, sleep latency, duration of sleep, sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. A general score between 0 and 21 is calculated from these individual scores. A score of >5 is defined as impaired sleep quality.

The Basic Nordic Sleep Questionnaire (BNSQ)[42] was used in two of our included studies.[1,36] It has been used widely in Nordic countries and is a validated tool for assessing subjective sleep complaints. A five-point scale [1–5] is used to indicate how often a symptom or complaint occurs.

The Epworth Sleepiness Scale (ESS) was used in four studies.[12,14,16,22] This is a self-administered questionnaire that assesses the general level of daytime sleepiness or sleep propensity. Participants score on a 0–3 scale how likely they will be to doze off during eight situations during a normal day. A total score of nine or higher indicates excessive sleepiness during the day.

Questionnaire results

The majority of studies found that individuals with SCI generally slept worse than healthy controls, and when comparing individuals with paraplegia and tetraplegia, the tetraplegics more often had poorer sleep quality. All results and the self-assessments of sleep in individuals with SCI are listed in Table 2.

Discussion

In this review we found that individuals with SCI suffer from several sleep-wake problems including: 1. Changes in sleep variables: PLMS indexes, sleep apnea and lower oxygenation levels; 2. Autonomic changes; 3. Neuroendocrine changes; 4. Poorer self-rated quality of sleep.

The studies featured an overall majority of male participants and when etiologies of the SCIs were reported, most of the causes were traumatic.

We now discuss the potential physiological mechanisms underlying the identified changes.

Changes in sleep variables

The PSG studies[7,9,11–13,15,16,20,28] show increased PLM and RLS levels, more sleep apnea and lowered oxygenation levels in individuals with SCI.

Previous research has indicated that RLS could be related to mesencephalic or other supraspinal neuroplastic changes, such as impaired dopaminergic regulation.[43] Further, the neurological explanation could be related to the underlying mechanisms of phantom sensations or by a similar neuroplasticity in the sleep/wake regulatory circuits of SCI rats.[44–46]

PLMS have a significantly higher prevalence in individuals with incomplete motor lesions than in individuals with complete lesions. In addition, the SCI populations have a high prevalence of PLMS, and many of the individuals present with PLMS during REM-sleep and wakefulness. These conditions might suggest the existence of a spinal cord central pattern generator of PLMS.[16,47,48]

The SDB in SCI populations is commonly obstructive, but individuals with SCI also experience episodes of central apnea. This is possibly a result of the weakened auxiliary respiratory muscles or a response to potentially respiratory-depressant medications.[49]

A relatively large study[49] of 50 tetraplegic patients investigated the pathogenesis of, and the factors predisposing to, sleep apnea. They also found a high prevalence (48%) of sleep apnea, and reported positive correlations between sleep apnea and age, BMI, neck circumference and time since injury. An important observation from their study was that most of the apneic participants had a low clinical suspicion of sleep apnea, since they were not obese, and only those suffering from severe apnea had daytime complaints. This might make it difficult to identify the problem in a daily clinical setting. The group emphasized the importance of systematic sleep assessments and follow-up examinations in this population.

A link between sleep apnea and cardiovascular morbidity and mortality has been suggested in able-bodied populations,[50,51] and the study of tetraplegic individuals by Stockhammer *et al.*[49] showed that the use of cardiac medications was also more common in individuals with an SDB. Burns *et al*.[38] made similar observations.

Future research should aim to determine whether there is an association between SDB and cardiac disease (ischemic and non-ischemic) in individuals with SCI, since cardiac disease is one of the primary causes of death in tetraplegic individuals.

Overall, the mechanisms responsible for RLS, PLMS and SDB have not been investigated thoroughly enough, and the most recent studies have proved inconclusive in terms of distinguishing between the level of lesion and the occurrence and severity of SDB. Further investigation is needed to clarify the underlying mechanisms of individuals' symptoms.

Autonomic changes

The maximum HR was lower in tetraplegic individuals than in controls,[24] and there was a loss of low-frequency 24-hour HRV in paraplegic and tetraplegic individuals compared with controls,[26] suggesting that these autonomic changes in SCI individuals are due to the loss of sympathetic tone.[52]

Individuals with SCI showed no day-to-night changes in leg flow or resistance, unlike what occurred in the controls investigated in this context.

Nocturnal penile tumescence differs significantly in cSCI individuals compared with tSCI individuals.[21,29] Penile tumescence is increased in REM sleep,[53] but the underlying mechanism has not been evaluated, so further research is needed to explain their findings properly.

High-amplitude propagating contractions of the colon are absent before, during and after sleep in SCI individuals, but are present in the CG.[25] This might be due to the loss of brain-gut control because of the SCI, but this also needs further investigation.

We have not come across any studies addressing urinary problems and sleep, but urinary problems are common among individuals with SCI. In an epidemiological study by Biering-Sørensen *et al*.[1] as many as 17.7% of the participants ranked problems with voiding as their primary problem with sleep. However, investigation of ADH in SCI individuals is the closest we have come to assessing urinary challenges. Further research on the impact of urinary and bowel problems on individuals' sleep might be beneficial.

Neuroendocrine changes

As mentioned above, ADH secretion is altered in individuals with SCI,[25] with no diurnal variations in serum ADH level or urine output, irrespective of whether the SCI was above or below T6. A probable explanation of this phenomenon is the pooling of blood in the lower extremities, leading to lower central venous pressure, which has been shown to enhance the ADH response to osmotic stimulation. Therefore, it is reasonable to suppose that paraplegic and tetraplegic individuals will benefit from the use of compression stockings and an abdominal binder in combination with restricted liquid intake.

Individuals with cSCI show altered circadian melatonin rhythms, unlike tSCI individuals and controls.[6,14,20] The recent study by Fatima *et al*.[6] of melatonin found significant differences in circadian variation between the CG and the SCIG, whereby melatonin levels in the cSCIG were significantly higher during morning hours and significantly lower during night hours, whereas a secretion pattern without any diurnal variations might have been expected, as was the case in the studies of Verheggen *et al*. and Scheer *et al*.[14,20] This suggests there are compensatory changes in cortisol due to the lack of melatonergic secretion. These findings also need further evaluation.

Previous studies[54,55] have shown that higher than physiological concentrations of melatonin in the blood are able to inhibit ADH in vivo. Pharmacological concentrations of melatonin have been able to stimulate ADH secretion *in vitro*.

Since melatonin and ADH secretion are both altered in individuals with SCI, it would be valuable to know the exact relationship between these two hormones in order to help individuals suffering from insomnia as well as those with nocturia.

The altered melatonin secretion in cSCI seems to be explained by the abruption of the neural pathway from the suprachiasmatic nuclei to the pineal gland, which passes through the cervical spinal cord.

Self-rated quality of sleep

Finally, SCI individuals tend to report worse subjective quality of sleep than able-bodied controls, and when compared with the level of injury, tetraplegic individuals often rate their sleep quality to be worse than do paraplegic individuals.

The aforementioned results coincide with the overall explanation that the symptoms and complications experienced by individuals with SCI are primarily caused by the loss of sympathetic innervation and the dominant parasympathetic control mediated by the vagal nerve in individuals with higher-level SCI, in particular that above T6.

January *et al*.[33] studied the sleep quality of 177 individuals with pediatric onset SCI. Unfortunately, the study did not fully meet our inclusion criteria for group comparisons, but they found that 51.4% of the participants had had sleep difficulties during the previous month. Even after controlling for age, injury level and pain, sleep quality explained a small but significant proportion of the variance in depression and anxiety. Increased age and tetraplegia were significantly associated with poor sleep.

Limitations and future research

When conducting our searches we found a few studies that were very relevant in our field of research, but which did not fully meet our inclusion criteria, so we excluded them.

The studies considered here have a number of limitations. First and foremost, sleep parameters may be influenced by medication. Many individuals with SCI are treated with different medications, and not all studies take this into consideration when interpreting their results. Also, known and unknown side effects may mimic or mask autonomic changes.

Second, the number of participants in the studies is usually small, which makes subgroup analyses (e.g. by level and completeness of SCI) difficult.

Lastly, when comparing questionnaire data in sleep research, there is a lack of consensus about the choice of questionnaire. Most sleep questionnaires are somewhat comparable overall, but in order to improve inter-study validation, this aspect of sleep research could be more standardized.

The PSQI questionnaire is widely used and seems to present few problems when used in different populations. On the other hand, when investigating daytime complaints, it might be useful to develop a standardized questionnaire other than the ESS that could be used in less active or immobile populations, since it is possible that several of the items in the ESS are not applicable to people with an SCI or those in similar conditions.

Conclusions

Significant differences were found between groups with SCI and able-bodied controls. In general, SCI has marked effects on individual's sleep, measured objectively and subjectively, but the detail of several aspects within this field of research need further investigation and more supportive studies.

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